

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : King, et al.

U.S. Serial No. : 10/593,217, National Stage Application of
International Application No.
PCT/US2005/010152, filed March 25, 2005,
claiming priority of U.S. Serial
No.60/556,565, filed March 26, 2004

Filed : September 15, 2006

Confirmation No.: 7034

Examiner : Not Yet Known

Art Unit : Not Yet Known

For : COMBINATION THERAPY COMPRISING
CLORETAZINE™

Law Offices of Albert Wai-Kit Chan, LLC
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141-07 20th Avenue
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April 30, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, Applicants would like to direct the Examiner's attention to the following references which are listed below and on Forms PTO/SB/08A and PTO/SB/08B (which are attached hereto as **Exhibit A**), and further attached as **Exhibits 1-20**.

Applicants would like to note that the listed references 1-14 are issued U.S. Patents and/or U.S. Publications. In addition, reference number 17 was cited by the examiner in related U.S. Patent No.

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6,855,695, issued February 15, 2005. Accordingly, pursuant to 37 CFR 1.98(d), a copy of these references is not required to be submitted with this SIDS. However, Applicants invites the Examiner to contact the Applicants' undersigned attorney's office if a copy of any of the listed references is desired.

1. U.S. Patent No. 4,175,200 November 20, 1979, Hunter, et al.,
"N, N-Disubstituted Sulfonyl Hydrazines"
2. U.S. Patent No. 4,385,055, May 24, 1983, Klayman, et al.,
"2-Acetyl-And 2-Propionylpyridine Thiosemicarbazones as
Antimalarials"
3. U.S. Patent No. 4,447,427, May 8, 1984, Klayman, et al., "2-
ACetyl-And 2-Propionylpyridine Thiosemicarbazones"
4. U.S. Patent No. 4,684,747, August 4, 1987, Satorelli, et
al., "N, N'-bis(sulfonyl)hydrazines Having Antineoplastic
Activity"
5. U.S. Patent No. 4,696,938, September 29, 1987, Satorelli,
Le, Dat P., "Insecticidal 6-aryl-pyridine
Thiosemicarbazones"
6. U.S. Patent No. 4,849,563, July 18, 1989, Satorelli, et al.,
"Novel 1-alkyl-1-arenesulfonyl-2-alkoxycarbonylsulfonyl
hydrazines Having Antineoplastic Activity"
7. U.S. Patent No. 5,101,072, March 31, 1992, Satorelli, et
al., "Sulfonylhydrazines and Their Uses as Antineoplastic
Agents and as Antitrypanosomal Agents"

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8. U.S. Patent No. 5,214,068, May 25, 1993, Satorelli, et al.,
"Sulfonylhydrazines and Their Uses as Antineoplastic Agents
and as Antitrypanosomal Agents"
9. U.S. Patent No. 5,256,820, October 26, 1993, Satorelli, et
al., "1-alkyl-2-acyl-1, 2-disulfonylhydrazines"
10. U.S. Patent No. 5,637,619, June 10, 1997, Satorelli, et
al., "Antitumor 2-aminocarbonyl-1, 2-bis(methylsulfonyl)-1-
(substituted)hydrazines"
11. U.S. Patent No. 5,767,134, June, 16, 1998, Li, et al.,
"Prodrug Forms of Ribonucleotide Reductase Inhibitors 3-AP
and 3-AMP"
12. U.S. Patent No. 6,040,338, March 21, 2000, Satorelli, et
al., "N, n-bis(sulfonyl)hydrazines Useful as Antineoplastic
Agents"
13. U.S. Patent No. 6,696,487, February 24, 2004, Gerusz, et
al., "Fungicidal Phenyl (thio) Urea and Phenyl (thio)
Cabamate Derivatives"
14. U.S. Patent No. 6,855,695, February 15, 2005, Xu, et al.,
"Water-Soluble Shps as Novel Alkylating Agents"
15. International Publication No. WO/2002/030424, April 18,
2002, Doyle, et al., "Modified Prodrug Forms of Ap/Amp"
[Exhibit 1]
16. Baumann RP, et al., 2004, "1,2-Bis(methylsulfonyl)-1-(2-
chloroethyl)-2-[(methylamino)carbonyl]hydrazine (VNP40101M):
II. Role of O6-alkylguanine-DNA alkyltransferase in

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cytotoxicity." Cancer Chemother Pharmacol. 53(4):288-295
[Exhibit 2]

17. Burchenal, et al., 1988, "Cancer: the Outlaw Cell," ed.
Richard E Lafond, American Chemical Society: 204-205

18. Gura, et al., 1997, "Systems for identifying new drugs are
often faulty," Science: 278(5340):1041-2 [Exhibit 3]

19. Lee, et al., 2002, "Toxicological evaluation of 1,2
bis("methylsulfonyl)-1-(2-chloroethyl)-
2(methylaminocarbonyl) hydrazine (VNP40101M), novel
alkylating Agent with Potential Antitumor Activity, with
Intravenous Administration in Rats and Dogs", International
Journal of Toxicology. Vol. 23: 23-39 [Exhibit 4]

20. Hrubiec, et al., 1986, "Synthesis and evaluation of 1-
(arylsulfonyl)-2-[(methoxycarbonyl)sulfonyl]-1
methylhydrazines ++ + as antineoplastic agents." J Med Chem.
29(9):1777-9 [Exhibit 5]

21. Hrubiec, et al., 1986, "Synthesis and evaluation of 2-
substituted 1-methyl-1-(4-tolylsulfonyl)hydrazines as
antineoplastic agents," J Med Chem. 29(7):1299-301 [Exhibit
6]

22. Murren, et al., 2005, "A phase I and pharmacokinetic study
of VNP40101M, a new alkylating agent, in patients with
advanced or metastatic cancer", Investigational New Drugs.
Vol 23: 123-135 [Exhibit 7]

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23. Mao, et al., 2002, "Pharmacokinetics, Mass Balance, and Tissue Distribution of a Novel DNA Alkylating Agent, VNP40101M, in Rats", AAPS PharmSci: 4(4)24 [Exhibit 8]
24. Penketh, et al., 1994, "Studies on the mechanism of decomposition and structural factors affecting the aqueous stability of 1,2-bis(sulfonyl)-1-alkylhydrazines", J Med Chem 37: 2912-2917 [Exhibit 9]
25. Penketh, et al., 2000, "Comparison of DNA lesions produced by tumor-inhibitory 1,2-bis(sulfonyl)hydrazines and chloroethylnitrosoureas", Biochem Pharmacol 59:283-91 [Exhibit 10]
26. Pratviel, et al., 1989, "Cytotoxic and DNA-damaging Effects of 1,2-bis(sulfonyl)hydrazines on Human Cells of the Mer+ and Mer- phenotype", Cancer Biochem Biophys 10:365-75 (abstract only) [Exhibit 11]
27. Shyam, et al., 1985, "Synthesis and evaluation of N,N'-bis(arylsulfonyl)hydrazines as antineoplastic agents" J Med Chem 28:525-7 [Exhibit 12]
28. Shyam, et al., 1986, "1,2-bis(arylsulfonyl)hydrazines. 2. The influence of arylsulfonyl and aralkylsulfonyl substituents on antitumor and alkylating activity", J Med Chem 29:1323-5 [Exhibit 13]
29. Shyam, et al., 1987, "1,2-Bis(sulfonyl)hydrazines. 3. Effects of structural modification on antineoplastic activity", J Med Chem 30:2157-61 [Exhibit 14]

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30. Shyam, et al., 1990, "Synthesis and evaluation of 1,2,2-tris(sulfonyl)hydrazines as antineoplastic and trypanocidal agents", J Med Chem. 33(8):2259-64 [Exhibit 15]
31. Shyam, et al., 1993, "Synthesis and evaluation of 1-acyl-1,2-bis(methylsulfonyl)-2-(2-chloroethyl)hydrazines as antineoplastic agents", J Med Chem 36:3496-502 [Exhibit 16]
32. Shyam, et al., 1996, Antitumor 2-(aminocarbonyl)-1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-hydrazines", J Med Chem 39:796-801 [Exhibit 17]
33. Giles, et al., 2004, "A Phase I and Pharmacokinetic Study of VNP40101M, a Novel Sulfonylhydrazine Alkylating Agent, in Patients with Refractory Leukemia.", Clinical Cancer Research, Vol. 10, Pages 2908-2917 [Exhibit 18]
34. Ishiguro, et al., 2005, "Role of O-alkylguanine-DNA alkyltransferase in the cytotoxic activity of cloreztatine", Mol Cancer Ther, Vol. 4 (11), Pages 1755-1763 [Exhibit 19]
35. Rice, et al., 2005, "Differential inhibition of cellular glutathione reductase activity by isocyanates generated from the antitumor prodrugs Cloretazine and BCNU." , Biochemical Pharmacology, Vol. 69, Pages 1463-1472 [Exhibit 20]

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If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Supplemental Information Disclosure Statement. However, if additional fees are required, authorization is given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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Exhibit A

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known

Application Number	10/593,217
Filing Date	September 15, 2006
First Named Inventor	KING, et al.
Art Unit	Not Yet Known
Examiner Name	Not Yet Known
Attorney Docket Number	891-A-PCT-US

U. S. PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	
	1	US- 4,175,200	11-20-1979	Hunter, et al.		
	2	US- 4,385,055	05-24-1983	Klayman, et al.		
	3	US- 4,447,427	05-08-1984	Klayman, et al.		
	4	US- 4,684,747	08-04-1987	Satorelli, et al.		
	5	US- 4,696,938	09-29-1987	Satorelli, et al.		
	6	US- 4,849,563	07-18-1989	Satorelli, et al.		
	7	US- 5,101,072	03-31-1992	Satorelli, et al.		
	8	US- 5,214,068	05-25-1993	Satorelli, et al.		
	9	US- 5,266,820	10-26-1993	Satorelli, et al.		
	10	US- 5,637,619	06-10-1997	Satorelli, et al.		
	11	US- 5,767,134	06-16-1998	Li, et al.		
	12	US- 6,040,338	03-21-2000	Satorelli, et al.		
	13	US- 6,696,487	02-24-2004	Gerusz, et al.		
	14	US- 6,855,695	02-15-2005	Xu, et al.		
		US-				
		US-				
		US-				
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FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁴
	15	WO/2002/030424	04-18-2002	Doyle, et al.		

Examiner Signature	Date Considered
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 808. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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Substitute for form 1449/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Application Number	10/593,217
		Filing Date	September 15, 2006
		First Named Inventor	KING, et al.
		Art Unit	Not Yet Known
		Examiner Name	Not Yet Known
Sheet 2	of 3	Attorney Docket Number	891-A-PCT-US

OTHER PRIOR ART—NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	16	Baumann RP, et al., 2004, "1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-[(methylamino)carbonyl]hydrazine (VNP40101M): II. Role of O6-alkylguanine-DNA alkyltransferase in cytotoxicity." Cancer Chemother Pharmacol. 53(4):288-295	
	17	Burchenal, et al., 1988, "Cancer: the Outlaw Cell," ed. Richard E Lafond, American Chemical Society: 204-205	
	18	Gura, et al., 1997, "Systems for identifying new drugs are often faulty." Science: 278(5340):1041-2	
	19	Lee, et al., 2002, "Toxicological evaluation of 1,2 bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine (VNP40101M), novel alkylating Agent with Potential Antitumor Activity, with Intravenous Administration in Rats and Dogs", International Journal of Toxicology. Vol. 23: 23-39	
	20	Hrubiec, et al., 1986, "Synthesis and evaluation of 1-(arylsulfonyl)-2-[(methoxycarbonyl)sulfonyl]-1-methylhydrazines ++ as antineoplastic agents." J Med Chem. 29(9):1771-9	
	21	Hrubiec, et al., 1986, "Synthesis and evaluation of 2-substituted 1-methyl-1-(4-tolylsulfonyl)hydrazines as antineoplastic agents," J Med Chem. 29(7):1299-301	
	22	Murren, et al., 2005, "A phase I and pharmacokinetic study of VNP40101M, a new alkylating agent, in patients with advanced or metastatic cancer", Investigational New Drugs. Vol 23: 123-135	
	23	Mao, et al., 2002, "Pharmacokinetics, Mass Balance, and Tissue Distribution of a Novel DNA Alkylating Agent, VNP40101M, in Rats", AAPS PharmSci: 4(4)24	
	24	Penketh, et al., 1994, "Studies on the mechanism of decomposition and structural factors affecting the aqueous stability of 1,2-bis(sulfonyl)-1-alkylhydrazines," J Med Chem 37: 2912-2917	
	25	Penketh, et al., 2000, "Comparison of DNA lesions produced by tumor-inhibitory 1,2-bis(sulfonyl)hydrazines and chloroethylnitrosoureas", Biochem Pharmacol 59:283-91	

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Complete if Known**INFORMATION DISCLOSURE
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Sheet 3

of 3

Application Number	10/593,217
Filing Date	September 15, 2006
First Named Inventor	KING, et al.
Art Unit	Not Yet Known
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OTHER PRIOR ART--NON PATENT LITERATURE DOCUMENTS

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	26	Pratviel, et al., 1989, "Cytotoxic and DNA-damaging Effects of 1,2-bis(sulfonyl)hydrazines on Human Cells of the Mer+ and Mer- phenotype", Cancer Biochem Biophys 10:365-75 (abstract only)	
	27	Shyam, et al., 1985, "Synthesis and evaluation of N,N-bis(arylsulfonyl)hydrazines as antineoplastic agents" J Med Chem 28:525-7	
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	29	Shyam, et al., 1987, "1,2-Bis(sulfonyl)hydrazines. 3. Effects of structural modification on antineoplastic activity", J Med Chem 30:2157-61	
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	31	Shyam, et al., 1993, "Synthesis and evaluation of 1-acyl-1,2-bis(methylsulfonyl)-2-(2-chloroethyl)hydrazines as antineoplastic agents", J Med Chem 36:3498-502	
	32	Shyam, et al., 1996, Antitumor 2-(aminocarbonyl)-1,2-bis(methylsulfonyl)-1-(2-chloroethyl)- hydrazines", J Med Chem 39:796-801	
	33	Giles, et al., 2004, "A Phase I and Pharmacokinetic Study of VNP40101M, a Novel Sulfonylhydrazine Alkylating Agent, in Patients with Refractory Leukemia.", Clinical Cancer Research, Vol. 10, Pages 2908-2917	
	34	Ishiguro, et al., 2005, "Role of O-alkylguanine-DNA alkyltransferase in the cytotoxic activity of cloretazine", Mol Cancer Ther, Vol. 4 (11), Pages 1755-1763	
	35	Rice, et al., 2005, "Differential inhibition of cellular glutathione reductase activity by isocyanates generated from the antitumor prodrugs Cloretazine and BCNU.", Biochemical Pharmacology, Vol. 69, Pages 1463-1472	

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